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USPT,JPAB,EPAB,DWPI	glaucoma	7491	L1

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☐ 1. Document ID: WO 9824932 A1

L4: Entry 1 of 1 File: EPAB Jun 11, 1998

PUB-NO: WO009824932A1
DOCUMENT-IDENTIFIER: WO 9824932 A1
TITLE: METHODS FOR DIAGNOSING GLAUCOMA AND DISCOVERING ANTI-GLAUCOMA DRUGS

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Display 20 Documents, starting with Document: 1

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L5: Entry 9 of 16 File: USPT Dec 29, 1998

DOCUMENT-IDENTIFIER: US 5854415 A
TITLE: Methods for the diagnosis of glaucoma

ABPL:
A glucocorticoid-induced protein, TIGR, that is produced by cells of the trabeclar meshwork can be used to diagnose glaucoma. The TIGR protein, anti-TIGR antibodies, and TIGR encoding sequences also provide a diagnostic for glaucoma and its related diseases.

GOPR:
The present invention is in the fields of diagnostics, and concerns methods and reagents for diagnosing glaucoma and related disorders. This invention was supported with Government funds (NIH EY02477 and NIH EY 08905-02). The Government has certain rights in this invention.

BSPR:
"Glaucomas" are a group of debilitating eye diseases that are the leading cause of preventable blindness in the United States and other developed nations. Primary Open Angle Glaucoma ("POAG") is the most common form of glaucoma. The disease is characterized by the degeneration of the trabecular meshwork, leading to obstruction of the normal ability of aqueous humor to leave the eye without closure of the space (e.g., the "angle") between the iris and cornea (see, Vaughn, D. et al., In: General Ophthamology, Appleton & Lange, Norwalk, Conn., pp. 213-230 (1992)). A characteristic of such obstruction in this disease is an increased intraocular pressure ("IOP"), resulting in progressive visual loss and blindness if not treated appropriately and in a timely fashion.

BSPR:
A link between the IOP response of patients to glucocorticoids and the disease of POAG has long been suspected. While only 5% of the normal population shows a high IOP increase (16 mm Hg) to topical glucocorticoid testing, over 90% of patients with POAG show this response. In addition, an open angle glaucoma may be induced by exposure to glucocorticoids. This observation has suggested that an increased or abnormal glucocorticoid response in trabecular cells may be involved in POAG (Zhan, G. L. et al., Exper. Eye Res. 54:211-218 (1992); Yun, A. J. et al., Invest. Ophthamol. Vis. Sci. 30:2012-2022 (1989); Clark, A. F., Exper. Eye Res. 55:265 (1992); Klemetti, A., Acta Ophthamol. 68:29-33 (1990); Knepper, P. A., U.S. Pat. No. 4,617,299).

BSPR:
The ability of glucocorticoids to induce a glaucoma-like condition has led to efforts to identify genes or gene products that would be induced by the cells of the trabecular meshwork in response to glucocorticoids (Polansky, J. R. et al., In: Glaucoma Update IV, Springer-Verlag, Berlin pp. 20-29 (1991)). Initial efforts using short-term exposure to dexamethasone revealed only changes in specific protein synthesis. Extended exposure to relatively high levels of dexamethasone was, however, found to induce the expression of related 66 kD and 55 kD proteins that could be visualized by gel electrophoresis (Polansky, J. R., et al., In: Glaucoma Update IV, Springer-Verlag, Berlin, pp. 20-29 (1991)). The induction kinetics of these proteins as well as their dose response characteristics were similar to the kinetics those that were required for steroid-induced IOP elevation in human subjects (Polansky, J. R. et al., In: Glaucoma Update IV, Springer-Verlag, Berlin, pp. 20-29 (1991)). Problems of aggregation and apparent instability or loss of protein in the purification process were obstacles in obtaining a direct protein sequence.

BSPR:
Because increased IOP is a readily measurable characteristic of glaucoma, the diagnosis of the disease is largely screened for by measuring intraocular pressure (tonometry) (Strong, N. P., Ophthal, Physiol. Opt. 12:3-7 (1992), Greve, M. et al., Can. J. Ophthamol. 28:201-206 (1993)). Unfortunately, because glaucomatous and normal pressure ranges overlap, such methods are of limited value unless multiple readings are obtained (Hitchings, R. A., Br. J. Ophthamol. 77:326 (1993); Tuck, M. W. et al., Ophthal. Physiol. Opt. 13:227-232 (1993); Vaughan, D. et al., In: General Ophthamology, Appleton & Lange, Norwalk, Conn. pp. 213-230 (1992); Vernon, S. A., Eye 7:134-137 (1993)). For this reason, additional methods, such as direct examination of the optic disk and determination of the extent of a patient's visual field loss are often conducted to improve the accuracy of diagnosis (Greve, M. et al., Can. J. Ophthamol. 28:201-206 (1993)).

BSPR:
In view of the importance of glaucoma, and the at least partial inadequacies of prior methods of diagnosis, it would be desirable to have an improved, more accurate method for diagnosing glaucoma. The present invention provides such improved diagnostic agents and methods.

BSPR:
The invention concerns a novel peptide sequence discovered to be highly induced by glucocorticoids in the endothelial lining cells of the human trabecular meshwork. The cDNA for this protein, the protein itself, molecules that bind to it, and nucleic acid molecules that encode it, provide improved methods and reagents for diagnosing glaucoma and related disorders, as well as for diagnosing other diseases or conditions, such as cardiovacsular, immunological, or other diseases or conditions

that affect the expression or activity of the protein. Indeed, the molecules of the present invention may be used to diagnose diseases or conditions which are characterized by alterations in the expression of extracellular proteins. In addition, due to its cellular functions and DNA binding properties, the molecules of the present invention may be used to diagnose diseases or conditions which are characterized those functions.

BSPR:
The invention also provides a method for diagnosing glaucoma in a patient which comprises determining whether the amount of a TIGR protein present in the trabecular meshwork of an eye of the patient exceeds the amount of that TIGR protein present in the trabecular meshwork of an eye of an individual who is not suffering from glaucoma, wherein the detection of an excessive amount of the TIGR protein is indicative of glaucoma.

BSPR:
The invention also provides a method for quantitatively or qualitatively determining the amount of a TIGR protein present in the trabecular meshwork of an eye of an individual, and determining whether that amount exceeds the amount of that TIGR protein present in the trabecular meshwork of an eye of an individual who is not suffering from glaucoma, wherein the detection of an excessive amount of the TIGR protein is indicative of glaucoma.

DEPR:
As indicated above, the trabecular meshwork has been proposed to play an important role in the normal flow of the aqueous, and has been presumed to be the major site of outflow resistance in glaucomatous eyes. Human trabecular meshwork (HTM) cells are endothelial like cells which line the outflow channels by which aqueous humor exits the eye; altered synthetic function of the cells may involve in the pathogenesis of steroid glaucoma and other types of glaucoma. Sustained steroid treatment of these cells are interesting because it showed major difference was observed when compared to 1-2 day glucocorticoid (GC) exposure, which appears relevant to the clinical onset of steroid glaucoma (1-6 weeks).

DEPR:
Despite decades of research, prior to the present invention, the molecular basis for glaucoma had not been determined (Snyder, R. W. et al., Exper. Eye Res. 57:461-468 (1993); Wiggs, J. L. et al., Genomics 21:299-303 (1994)).

DEPR:
The II.2 clone is 2.0 Kb whereas the Northern blotting shows a band of 2.5 Kb. Although not including a poly A tail, the 3' end of the clone contains two consensus polyadenylation signals. Southern analysis suggested two groups of genomic sequences and two genomic clones were isolated. In-situ hybridization using these genomic probes shows that the TIGR gene and/or a sequence or sequences that specifically hybridize to the TIGR gene are located on chromosome 1, p36 and 10.11 or

12, p13, p15. Further in-situ hybridization using the P.sub.1 TIGR clone (P.sub.1 TIGR DNA was deposited on May 14, 1996, American Type Culture Collection, 12301 Parklawn Drive, Rockville, Md. 20852, USA) shows an additional TIGR gene and/or a sequence or sequences that specifically hybridize to the TIGR gene located at chromosome 1, q20-26, and most preferably at chromosome 1, q23-24. Clone P.sub.1 TIGR comprises human genomic sequences that specifically hybridize to the TIGR gene cloned into the BamHI site of vector pCYPAC (Ioannou et al., Nature Genetics, 6:84-89 (1994) herein incorporated by reference). Study of cyclohexamide treatment in the absence and presence of GC suggest that the induction of TIGR may involve factors in addition to the GC receptor. The TIGR gene may be involved in the cellular stress response since it is also induced by stimulants such as H.sub.2 O.sub.2, TPA, glucose and heat; this fact may relate to glaucoma pathogenesis and treatment.

DEPR:
The TIGR protein also contains 5 putative O-linked glycosylation sites throughout the molecule. "Leucine zipper" regions define a helical structure that permits protein-protein binding to occur (see, generally, Tso, J. Y. et al., PCT Patent Application WO93/11162; Land, K. H. et al., PCT Patent Application WO/93/191761). The TIGR protein contain 7 leucine zipper units. The presence of the zipper regions provides a means for the TIGR molecules to bind to one another forming macromolecular and possible aggregation. Studies showing the binding of this molecule to HTM cells (but not to fibroblast cells) support the notion that is can influence the outflow pathway in HTM tissue to cause the increased intra-ocular pressure that characterizes glaucoma and its related diseases. TIGR protein has also been successfully expressed using the baculovirus system and Sf9 insect cells. The major recombinant proteins are the two 55 kd cellular proteins encoded by the TIGR cDNA. Antibodies produced from these protein recognize both the cellular 55 kD proteins and the secreted 66 kD glycosylated form of these proteins in dexamethasome-treated HTM cells and in organ culture systems. In situ analysis of glaucomatous tissue specimens show a high expression level of this protein relative to normal controls.

DEPR:
The presence, induction, and level of the TIGR secretory protein mirror the onset and kinetics with which glucocorticoids induce glaucoma, and the glucocorticoid-induced expression of this secretory protein comprises the molecular basis for glaucoma and its related diseases. Such an understanding of the molecular basis permits the definition of diagnostic agents for glaucoma and its related diseases.

DEPR:
As used herein, the term "glaucoma" has its art recognized meaning, and includes both primary glaucomas, secondary glaucomas, and familial (i.e. inherited glaucomas). The methods of the present invention are particularly relevant to the diagnosis of POAG, OAG, juvenile glaucoma, and inherited

glaucomas. A disease or condition is said to be related to glaucoma if it possesses or exhibits a symptom of glaucoma, for example, an increased intra-ocular pressure resulting from aqueous outflow resistance (see, Vaughan, D. et al., In: General Ophthamology, Appleton & Lange, Norwalk, Conn., pp. 213-230 (1992)). The preferred agents of the present invention are discussed in detail below.

DEPR:
The agents of the present invention are capable of being used to diagnose the presence or severity of glaucoma and its related diseases in a patient suffering from glaucoma (a "glaucomatous patient"). Such agents may be either naturally occurring or non-naturally occurring. As used herein, a naturally occurring molecule may be "substantially purified," if desired, such that one or more molecules that is or may be present in a naturally occurring preparation, containing that molecule will have been removed or will be present at a lower concentration than that at which it would normally be found.

DEPR:
In one embodiment, such nucleic acid molecules will encode all or a fragment of TIGR protein, its "promoter" or flanking gene sequences. As used herein, the term "promoter" is used in an expansive sense to refer to the regulatory sequence(s) that control mRNA production. Such sequences include RNA polymerase binding sites, glucocorticoid response elements, enhancers, etc. All such TIGR molecules may be used to diagnose the presence of glaucoma and severity of glaucoma.

DEPR:
One aspect of the present invention concerns antibodies, single-chain antigen binding molecules, or other proteins that specifically bind to TIGR protein and its analogs, fusions or fragments. Such antibodies are "anti-TIGR antibodies," and may be used to diagnose glaucoma and its related diseases. As used herein, an antibody or peptide is said to "specifically bind" to TIGR if such binding is not competitively inhibited by the presence of non-TIGR molecules.

DEPR:
Nucleic acid molecules that encode all or part of the TIGR protein can be expressed, via recombinant means, to yield TIGR protein or peptides that can in turn be used to elicit antibodies that are capable of binding TIGR. Such antibodies may be used in immunodiagnostic assays of glaucoma. Such TIGR-encoding molecules, or their fragments may be a "fusion" molecule (i.e. a part of a larger nucleic acid molecule) such that, upon expression, a fusion protein is produced.

DEPR:
The ability to produced antibodies that bind TIGR molecules permits the identification of mimetic compounds of TIGR. A "mimetic compound" of TIGR is a compound that is not TIGR, or a fragment of TIGR, but which nonetheless exhibits an ability to specifically find to anti-TIGR antibodies. Such molecules can be used to elicit anti-TIGR antibodies, and thus, may be used

to assist the diagnosis of glaucoma and its related diseases.

DEPR:
A particularly desired use of the present invention relates to the diagnosis of glaucoma, POAG, pigmentary glaucoma, high tension glaucoma and low tension glaucoma and their related diseases. As used herein the term "glaucoma" refers to glaucoma, POAG, pigmentary glaucoma, and low tension glaucoma and their related diseases. As indicated above, methods for diagnosing glaucoma suffer from inaccuracy, or require multiple examinations. The molecules of the present invention may be used to define superior assays for glaucoma. Quite apart from such usage, the molecules of the present invention may be used to diagnosis or protect an individual's sensitivity to elevated intraocular pressure upon administration of steroids such as glucocorticoids or corticosteroids). Dexamethasone, cortisol and prednisolone are preferred steroids for this purpose. Medical conditions such as inflammatory and allergic disorders, as well as organ transplantation recipients, benefit from treatment with glucocorticoids. Certain individuals exhibit an increased sensitivity to such steroids (i.e., "steroid sensitivity"), which is manifested by an undesired increase in intraocular pressure. The present invention may be employed to diagnosis or predict such sensitivity, as well as glaucoma and related diseases.

DEPR:
In a first embodiment, the TIGR molecules of the present invention are used to determine whether an individual has a mutation affecting the level (i.e., the concentration of TIGR mRNA or protein in a sample, etc.) or pattern (i.e., the kinetics of expression, rate of decomposition, stability profile, etc.) of the TIGR expression (collectively, the "TIGR Response" of a cell or bodily fluid) (for example, a mutation in the TIGR gene, or in a regulatory region(s) or other gene(s) that control or affect the expression of TIGR), and being predictive of individuals who would be predisposed to glaucoma, related diseases, or steroid sensitivity. As used herein, the TIGR Response manifested by a cell or bodily fluid is said to be "altered" if it differs from the TIGR Response of cells or of bodily fluids of normal individuals. Such alteration may be manifested by either abnormally increased or abnormally diminished TIGR Response. To determine whether a TIGR Response is altered, the TIGR Response manifested by the cell or bodily fluid of the patient is compared with that of a similar cell sample (or bodily fluid sample) of normal individuals. As will be appreciated, it is not necessary to re-determine the TIGR Response of the cell sample (or bodily fluid sample) of normal individuals each time such a comparison is made; rather, the TIGR Response of a particular individual may be compared with previously obtained values of normal individuals.

DEPR:
In one sub-embodiment, such an analysis is conducted by determining the presence and/or identity of polymorphism(s) in the TIGR gene or its flanking regions which are associated with glaucoma, or a predisposition to glaucoma, related diseases, or

steroid sensitivity.

DEPR:
Other known nucleic acid amplification procedures, such as allele-specific oligomers, branched DNA technology, transcription-based amplification systems, or isothermal amplification methods may also be mused to amplify and analyze such polymorphisms (Malek, L. T. et al., U.S. Pat. No. 5,130,238; Davey, C. et al., European Patent Application 329,822; Schuster et al., U.S. Pat. No. 5,169,766; Miller, H. I. et al., PCT appln. WO 89/06700; Kwoh, D. et al., Proc. Natl. Acad. Sci. (U.S.A.) 86:1173 (1989); Gingeras, T. R. et al., PCT application WO 88/10315; Walker, G. T. et al., Proc. Natl. Acad. Sci. (U.S.A.) 89:392-396 (1992)). All the foregoing nucleic acid amplification methods coupled be used to predict or diagnose glaucoma.

DEPR:
The identification of a polymorphism in the TIGR gene can be determined in a variety of ways. By correlating the presence or absence of glaucoma in an individual with the presence or absence of a polymorphism in the TIGR gene or its flanking regions, it is possible to diagnose the predisposition of an asymptomatic patient to glaucoma, related diseases, or steroid sensitivity. If a polymorphism creates or destroys a restriction endonuclease cleavage site, or if it results in the loss or insertion of DNA (e.g., a VNTR polymorphism), it will alter the size or profile of the DNA fragments that are generated by digestion with that restriction endonuclease. As such, individuals that possess a variant sequence can be distinguished from those having the original sequence by restriction fragment analysis. Polymorphisms that can be determined in this manner are termed "restriction fragment length polymorphisms" ("RFLPs"). RFLPs have been widely used in human and animal genetic analyses (Glassberg, J., UK patent Application 2135774; Skolnick, M. H. et al., Cytogen. Cell GEnet. 32:58-67 (1982); Botstein, D. et al., Ann. J. Hum. Genet. 32:314-331 (1980); Fischer, S. G et al. (PCT Application WO90/13668); Uhlen, M., PCT Application WO90/11369)). The role of TIGR in glaucoma pathogenesis indicates that the presence of genetic alterations (e.g., DNA polymorphisms) that affect the TIGR Response can be employed to predict glaucoma.

DEPR:
In accordance with this embodiment of the invention, a sample DNA is obtained from a patient's cells. In a preferred embodiment, the DNA sample is obtained from the patient's blood. However, any source of DNA may be used. The DNA is subjected to restriction endonuclease digestion. TIGR is used as a probe in accordance with the above-described RFLP methods. By comparing the RFLP pattern of the TIGR gene obtained from normal and glaucomatous patients, one can determine a patient's predisposition to glaucoma. The polymorphism obtained in this approach can then be cloned to identify the mutation at the coding region which alters the protein's structure or regulatory region of the gene which affects its expression level. Changes involving promoter interactions with other

regulator proteins can be identified by, for example, gel shift assays using HTM cell extracts, fluid from the anterior chamber of the eye, serum, etc. Interactions of TIGR protein in glaucomatous cell extracts, fluid from the anterior chamber of the eye, serum, etc. can be compared to control samples to thereby identify changes in those properties of TIGR that relate to the pathogenesis of glaucoma. Similarly such extracts and fluids as well as others (blood, etc.) can be used to diagnosis or predict steroid sensitivity.

DEPR:
In a second embodiment, the previously described "anti-TIGR antibodies" are employed in an immunodiagnostic assay for glaucoma and its related diseases.

DEPR:
As discussed above, TIGR protein is secreted extracellularly from the trabecular meshwork into the extracellular matrix of the trabecular meshwork, and thus may pass out into the body fluids. This characteristic permits one to assay TIGR concentrations in blood, lymph, or serum, and to thereby determine whether a patient's TIGR levels exceed those found in the blood of individuals who do not have glaucoma and are not predisposed to glaucoma related diseases or steroid sensitivity. Patients found to have altered levels of TIGR thus may be diagnosed as glaucoma.

DEPR:
Thus, a third aspect of the present invention concerns the recognition that one can diagnosis or predict glaucoma, related diseases or steroid sensitivity by determining the TIGR Response of cells or tissue other than the trabecular meshwork.

DEPR:
In one sub-embodiment of this aspect of the present invention, one can diagnose or predict glaucoma, related diseases and steroid sensitivity by ascertaining the TIGR Response in a biopsy (or a macrophage or other blood cell sample), or other cell sample, or more preferably, in a sample of bodily fluid (especially, blood, serum, plasma, tears, etc.). Since the TIGR gene is induced in response to the presence of glucocorticoids, a highly preferred embodiment of this method comprises ascertaining such TIGR Response prior to, during and/or subsequent to, the administration of a glucocorticoid. Thus, by way of illustration, glaucoma could be diagnosed or predicted by determining whether the administration of a glucocorticoid (administered topically, intraocularly, intramuscularly, systemically, or otherwise) alters the TIGR Response of a particular individual, relative to that of normal individuals. Most preferably, for this purpose, at least a "TIGR gene-inducing amount" of the glucocorticoid will be provided. As used herein, a TIGR gene-inducing amount of a glucocorticoid is an amount of glucocorticoid sufficient to cause a detectable indication of TIGR expression in cells of glaucomatous or non-glaucomatous individuals.

DEPR:
In an alternative diagnostic format, ocular tissue (obtained, for example by trabeculotomy) may be evaluated in an in situ immunodiagnostic assay for glaucoma and its related diseases.

DEPR:
In such a format, antibodies (especially labeled antibodies) or other TIGR-binding peptide are incubated in the presence of ocular tissue in order to evaluate the clinical degree and significance of glaucoma in biopsied tissue. The extent, location, or degree of TIGR in the ocular tissue is determined by staining or other visualization methods. Such information is then compared to the staining pattern obtained from normal or glaucomatous individuals in order to diagnose or predict glaucoma.

DEPR:
As discussed above, TIGR protein exhibits an ability to self-aggregate, due at least in part to the presence of leucine zippers in the molecule. Because small peptide fragments of TIGR that possess such zipper regions can bind to TIGR, such peptides may be used as alternatives to anti-TIGR antibodies in diagnostic assays. The use of such peptides is desirable since the peptides can be modified to possess both lipophilic and hydrophilic groups. The presence of such groups will permit the peptide to traverse the corneal membrane. Thus, such agents may be provided topically in an eye drop or ointment, and can be used in the same manner as anti-TIGR antibodies to effect the diagnosis of glaucoma. The peptide will desirably be labeled with a fluorescent group to facilitate detection.

DEPR:
Northern analysis showed clone TIGR to be approximately 2.5 kb, and to encode a protein of unique sequence. The induction of the mRNA required protein synthesis and insulin-like growth factor reduced the induction effect by 50%. The TIGR mRNA indication was not observed in dexamethasone treated fibroblasts, keratinocytes, or ciliary epithelial cells. The pattern of induction in HTM cells was distinguishable from other steroid induced proteins such as metallothionine, alpha.sub.1 -acid glycoprotein, and TAT which were maximally induced by one day dexamethasone treatment. In addition to dexamethasone, the TIGR mRNA was induced in HTM cells exposed to hydrogen peroxide, TPA, or glucose for 3-24 hours. Dexamethasone treatment produced substantial loss in the mRNAs for glucocorticoid receptors and heat shock proteins (e.g., hsp 90 mRNA levels fell approximately 20 fold after 10 days of dexamethasone treatment).

DEPC:
III. Uses of the Molecules of the Invention in the Diagnosis of Glaucoma and Related Diseases

ORPL:
Stone et al., "Identification of a Gene that Causes Primary Open Angle Glaucoma", Science 275:668-670 (1997).

ORPL:
Clark, A.F., "Evaluation of Anti-Glaucoma Compounds and Discovery of Pathogenic Mechanisms using Perfusion Cultured Human Eyes," Exper. Eye Res. 55Ab266 (1992).

ORPL:
Zhan, G.L., et al., Steroid Glaucoma: Corticosteroid-Induced Ocular Hypertension in Cats, Exper. Eye Res. 54:211-218 (1992).

ORPL:
Nguyen, T.D. et al., "Molecular Biology Studies of Steroid-Induced Glaucoma Model Using Cultured Human Trabecular Meshwork," Invest Ophthalmol Vis. Sci. 32789 (1991).

ORPL:
Polansky, J.R., et al., "In Vitro Correlates of Glucocorticoid Effects on Intraocular Pressure," In: Glaucoma Update IV, Springer-Verlag, Berlin, pp. 20-29 (1991).

ORPL:
Weinreb, R.N., et al., "Detection of Glucocorticoid Receptors in Cultured Human Trabecular Cells," Invest Ophthalmol. Vis. Sci. 21:403-407 (1981).

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L5: Entry 10 of 16 File: USPT Aug 4, 1998

US-PAT-NO: 5789169
DOCUMENT-IDENTIFIER: US 5789169 A

TITLE: Methods for the diagnosis of glaucoma

DATE-ISSUED: August 4, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Huang; Weidong	Irvine	CA	N/A	N/A

US-CL-CURRENT: 435/6; 435/7.1, 435/91.2

CLAIMS:

What is claimed is:
1. A method for diagnosing glaucoma in a patient which comprises determining whether the amount of the secretory protein encoded by clone II.2 present in the trabecular meshwork of an eye of said patient exceeds the amount of said protein present in the trabecular meshwork of an eye of an individual who does not have glaucoma and is not predisposed to have glaucoma, wherein the detection of an altered amount of said protein is indicative of glaucoma.
2. The method of claim 1, wherein said determination is accomplished by determining the amount of an mRNA molecule that encodes the secretory protein of clone II.2 present in cells of the trabecular meshwork.
3. The method of claim 1, wherein said determination is accomplished by administering an antibody capable of specifically binding to the secretory protein encoded by clone II.2 to said patient and determining the extent to which said antibody binds to the extracellular matrix of the trabecular meshwork.
4. The method of claim 1, wherein said determination is accomplished by administering a peptide that binds the secretory protein encoded by clone II.2 of said patient and determining the extent to which said peptide binds to the extracellular matrix of the trabecular meshwork.
5. A method for diagnosing glaucoma in a patient under evaluation for suspected glaucoma which comprises assaying the concentration of a molecule, whose concentration is dependent upon the expression of a gene that encodes the secretory

protein of clone II.2, said molecule being present in a sample of cells or bodily fluid of said patient, in comparison to the concentration of that molecule present in a sample of cells or bodily fluid of an individual who does not have glaucoma and is not predisposed to have glaucoma, wherein an assayed concentration of said molecule is different from the assayed concentration of said molecule found in said individual who does not have glaucoma and is not predisposed to have glaucoma is diagnostic of glaucoma in said patient.

6. The method of claim 5, wherein said bodily fluid is selected from the group consisting of glaucomatous cell extract, fluid from the anterior chamber of the eye, blood, lymph and serum.

7. The method of claim 5, wherein said molecule is a protein molecule expressed by said gene.

8. The method of claim 5, wherein said molecule is an mRNA molecule encoded by said gene, or a cDNA molecule encoded by said gene.

9. The method of claim 8, wherein said concentration of said mRNA molecule is assayed by incubating a sample of said bodily fluid in the presence of a nucleic acid molecule that hybridizes to said mRNA molecule.

10. The method of claim 5, wherein prior to performing said assay, said patient is provided with a gene that encodes the secretory protein of clone II.2-inducing amount of a glucocorticoid; and wherein said comparison is made between the concentration of said molecule in said sample of cells or bodily fluid of said patient, and the concentration of said molecule in a sample of cells or bodily fluid of an individual who does not have glaucoma and is not predisposed to have glaucoma, but who has also received said gene-inducing amount of a said glucocorticoid.

11. The method of claim 10, wherein said molecule is an mRNA molecule encoded by said gene, or a cDNA molecule encoded by said gene.

12. The method of claim 10, wherein said molecule is a protein molecule expressed by said gene.

13. The method of claim 7, wherein said expression of said gene is assayed by incubating a sample of said cells or said bodily fluid in the presence of antibodies elicited in response to immunization of an antibody-producing cell with a recombinantly produced secretory protein encoded by clone II.2, wherein said antibody molecule binds the secretory protein encoded by clone II.2.

14. The method of claim 13, wherein said antibodies recognize a protein molecule expressed by steroid-treated human trabecular cells.

15. A method for diagnosing glaucoma in a patient which comprises the steps:

(A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, said marker nucleic acid molecule comprising a nucleotide sequence of a polynucleotide that specifically hybridizes to a polynucleotide that is linked to a gene that encodes the secretory protein of clone II.2, and a complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient, wherein nucleic acid hybridization between said marker nucleic acid molecule, and said complementary nucleic acid molecule obtained from said

patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting the level or pattern of said secretory protein of clone II.2 in said patient;
(B) permitting hybridization between said marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient; and
(C) detecting the presence of said polymorphism, wherein the detection of said polymorphism is diagnostic of glaucoma.
16. The method of claim 15, wherein said level of said secretory protein of clone II.2 is predictive.
17. The method of claim 15, wherein said pattern of said secretory protein of clone II.2 is predictive.
18. The method of claim 15, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is genetically linked to said gene, and has the sequence of a polynucleotide of chromosome 1, q.
19. The method of claim 18, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is genetically linked to said gene, and has the sequence of a polynucleotide of chromosome 1, q21-26.
20. The method of claim 19, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is genetically linked to said gene, and has the sequence of a polynucleotide of chromosome 1, q23-24.
21. The method of claim 15, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is physically linked to within 1 mb of said gene.
22. The method of claim 15, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is physically linked to within 100 kb of said gene.
23. The method of claim 15, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is physically linked to within 10 kb of said gene.
24. The method of claim 15, wherein said marker nucleic acid molecule comprises a nucleic acid molecule that encodes the secretory protein of clone II.2 or fragment thereof.
25. The method of claim 15, wherein said bodily fluid is selected from the group consisting of glaucomatous cell extract, fluid from the anterior chamber of the eye, blood, lymph and serum.
26. The method of claim 15, wherein said complementary nucleic acid molecule obtained from a cell or present in a bodily fluid of said patient is expressed by steroid-treated cells.
27. The method of claim 27, wherein said bodily fluid is ocular aqueous, and wherein said cells are HTM cells.
28. A method for diagnosing glaucoma in a patient which comprises the steps:
(A) obtaining a sample of cells or bodily fluid from said patient;
(B) determining whether said sample contains the secretory protein encoded by clone II.2 whose presence is predictive of a mutation affecting the level or pattern of said protein in said patient; wherein the detection of said protein is diagnostic for glaucoma.
29. A method for diagnosing steroid sensitivity in a patient under evaluation for suspected steroid sensitivity which comprises the steps:

(A) obtaining a sample of cells or bodily fluid from said patient;
(B) assaying said sample to determine the concentration of a molecule, whose concentration is dependent upon the expression of a gene that encodes the secretory protein of clone II.2, in comparison to the concentration of that molecule present in a sample of cells or bodily fluid of an individual who does not have steroid sensitivity and is not predisposed to have steroid sensitivity, wherein an assayed concentration of said molecule is different from the assayed concentration of said molecule found in said individual who does not have steroid sensitivity and is not predisposed to have steroid sensitivity is diagnostic of steroid sensitivity in said patient.
30. The method of claim 29, wherein said bodily fluid is selected from the group consisting of fluid from the anterior chamber of the eye, blood, lymph and serum.
31. The method of claim 30, wherein said molecule is an mRNA molecule encoded by said gene, or a cDNA molecule encoded by said gene.
32. The method of claim 31, wherein said concentration of said mRNA molecule is assayed by incubating a sample of said bodily fluid in the presence of a nucleic acid molecule that hybridizes to said mRNA molecule.
33. The method of claim 29, wherein said molecule is a protein molecule expressed by said gene.
34. The method of claim 30, wherein prior to performing said assay, said patient is provided with a gene that encodes the secretory protein of clone II.2-inducing amount of a glucocorticoid; and wherein said comparison is made between the concentration of said molecule in said sample of cells or bodily fluid of said patient, and the concentration of said molecule in a sample of cells or bodily fluid of an individual who does not have steroid sensitivity and is not predisposed to have steroid sensitivity, but who has also received said gene-inducing amount of a said glucocorticoid.
35. A method for diagnosing steroid sensitivity in a patient which comprises the steps:
(A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, said marker nucleic acid molecule comprising a nucleotide sequence of a polynucleotide that specifically hybridizes to a polynucleotide that is linked to a gene that encodes the secretory protein of clone II.2, and a complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient, wherein nucleic acid hybridization between said marker nucleic acid molecule, and said complementary nucleic acid molecule obtained from said patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting the level or pattern of said secretory protein of clone II.2 in said patient;
(B) permitting hybridization between said marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient; and
(C) detecting the presence of said polymorphism, wherein the detection of said polymorphism is diagnostic of steroid sensitivity.
36. The method of claim 35, wherein said level of said secretory protein of clone II.2 is predictive.

37. The method of claim 35, wherein said pattern of said secretory protein of clone II.2 is predictive.
38. The method of claim 35, wherein said complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient has been amplified using a nucleic acid amplification method.
39. The method of claim 38, wherein said nucleic acid amplification method is polymerase chain amplification.
40. The method of claim 38, wherein said nucleic acid amplification method is ligase chain reaction.
41. The method of claim 38, wherein said nucleic acid amplification method is oligonucletide ligation assay.
42. The method of claim 35, wherein said detecting the presence of said polymorphism is by allelic specific oligomers.
43. The method of claim 35, wherein said detecting the presence of said polymorphism is by branched DNA technology.
44. The method of claim 38, wherein said nucleic acid amplification method is transcription base amplification.
45. The method of claim 38, wherein said nucleic acid amplification method is iso thermal amplification.
46. The method of claim 15, wherein said complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient has been amplified using a nucleic acid amplification method.
47. The method of claim 46, wherein said nucleic acid amplification method is polymerase chain amplification.
48. The method of claim 46, wherein said nucleic acid amplification method is ligase chain reaction.
49. The method of claim 46, wherein said nucleic acid amplification method is oligonucletide ligation assay.
50. The method of claim 15, wherein said detecting the presence of said polymorphism is by allelic specific oligomers.
51. The method of claim 15, wherein said detecting the presence of said polymorphism is by branched DNA technology.
52. The method of claim 46, wherein said nucleic acid amplification method is transcription base amplification.
53. The method of claim 46, wherein said nucleic acid amplification method is iso thermal amplification.
54. A method for diagnosing glaucoma in a patient which comprises the steps:
(A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, said marker nucleic acid molecule comprising a nucleotide sequence of a polynucleotide that specifically hybridizes to a polynucleotide that is linked to a sequence that specifically hybridizes to a gene that encodes the secretory protein of clone II.2, and a complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient, wherein nucleic acid hybridization between said marker nucleic acid molecule, and said complementary nucleic acid molecule obtained from said patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting the level or pattern of said secretory protein of clone II.2 in said patient;
(B) permitting hybridization between said marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient; and
(C) detecting the presence of said polymorphism, wherein the

detection of said polymorphism is diagnostic of glaucoma.
55. The method of claim 54, wherein said level of said secretory protein of clone II.2 is predictive.
56. The method of claim 54, wherein said pattern of said secretory protein of clone II.2 is predictive.
57. The method of claim 54, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is genetically linked to a sequence that specifically hybridizes to said gene, and has the sequence of a polynucleotide of chromosome 1, q.
58. The method of claim 57, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is genetically linked to said gene, and has the sequence of a polynucleotide of chromosome 1, q21-26.
59. The method of claim 58, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is genetically linked to a sequence that specifically hybridizes to said, and has the sequence of a polynucleotide of chromosome 1, q23-24.
60. The method of claim 54, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is physically linked to within 1 mb of a sequence that specifically hybridizes to said gene.
61. The method of claim 54, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is physically linked to within 100 kb to a sequence that specifically hybridizes to said gene.
62. The method of claim 54, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is physically linked to within 10 kb to a sequence that specifically hybridizes to said gene.
63. The method of claim 54, wherein said marker nucleic acid molecule comprises a sequence that specifically hybridizes to said gene-encoding nucleic acid molecule, or fragment thereof.
64. The method of claim 54, wherein said bodily fluid is selected from the group consisting of glaucomatous cell extract, fluid from the anterior chamber of the eye, blood, lymph and serum.
65. The method of claim 54, wherein said complementary nucleic acid molecule obtained from a cell or present in a bodily fluid of said patient is expressed by steroid-treated cells.
66. The method of claim 54, wherein said bodily fluid is ocular aqueous, and wherein said cells are HTM cells.
67. A method for diagnosing glaucoma in a patient under evaluation for suspected glaucoma which comprises assaying the concentration of a molecule, whose concentration is dependent upon the expression of a gene, said gene having a nucleic acid sequence which specifically hybridizes to SEQ ID NO: 3 and which encodes for a glucocorticoid inducible 66 kD glycosylated protein and a glucocorticoid inducible 55 kD protein, said molecule being present in a sample of cells or bodily fluid of said patient, in comparison to the concentration of that molecule present in a sample of cells or bodily fluid of an individual who does not have glaucoma and is not predisposed to have glaucoma, wherein an assayed concentration of said molecule is different from the assayed concentration of said molecule in said individual who does not have glaucoma and is

not predisposed to have glaucoma is diagnostic of glaucoma in said patient.
68. The method of claim 67, wherein said bodily fluid is selected from the group consisting of glaucomatous cell extract, fluid from the anterior chamber of the eye, blood, lymph and serum.
69. The method of claim 67, wherein said molecule is a protein molecule expressed by said gene.
70. The method of claim 67, wherein said molecule is an mRNA molecule encoded by said gene, or a cDNA molecule encoded by said gene.
71. The method of claim 70, wherein said concentration of said mRNA molecule is assayed by incubating a sample of said bodily fluid in the presence of a nucleic acid molecule that hybridizes to said mRNA molecule.
72. The method of claim 69, wherein said expression of said gene is assayed by incubating a sample of said cells or said bodily fluid in the presence of antibodies elicited in response to immunization of an antibody-producing cell with a protein selected from the group consisting of a recombinantly produced glucocorticoid inducible 66 kD glycosylated protein, and recombinantly produced glucocorticoid inducible 55 kD protein, wherein said antibody molecule binds said recombinantly produced glucocorticoid inducible 66 kD glycosylated protein or said recombinantly produced glucocorticoid inducible 55 kD protein.
73. The method of claim 72, wherein said antibodies recognize a protein molecule expressed by steroid-treated human trabecular cells.
74. A method for diagnosing glaucoma in a patient which comprises the steps:
(A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, said marker nucleic acid molecule comprising a nucleic acid molecule that is linked to a gene, said gene having a nucleic acid sequence which specifically hybridizes to SEQ ID NO: 3 and which encodes for a glucocorticoid inducible 66 kD glycosylated protein and a glucocorticoid inducible 55 kD protein, and a complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient, wherein nucleic acid hybridization between said marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting the level or pattern of said glucocorticoid inducible 66 kD glycosylated protein or said glucocorticoid inducible 55 kD protein in said patient;
(B) permitting hybridization between said marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient; and
(C) detecting the presence of said polymorphism, wherein the detection of said polymorphism is diagnostic of glaucoma.
75. The method of claim 74, wherein said level is predictive.
76. The method of claim 74, wherein said pattern is predictive.

77. The method of claim 74, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is genetically linked to said gene, and has the sequence

of a polynucleotide of chromosome 1, q.
78. The method of claim 77, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is genetically linked to said gene, and has the sequence of a polynucleotide of chromosome 1, q21-26.
79. The method of claim 78, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is genetically linked to said gene, and has the sequence of a polynucleotide of chromosome 1, q23-24.
80. The method of claim 74, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is physically linked to within 1 mb of said gene.
81. The method of claim 74, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is physically linked to within 100 kb of said gene.
82. The method of claim 74, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is physically linked to within 10 kb of said gene.
83. The method of claim 74, wherein said marker nucleic acid molecule comprises a nucleic acid sequence which specifically hybridizes to SEQ ID NO: 3 and which encodes for a glucocorticoid inducible 66 kD glycosylated protein or fragment thereof and a glucocorticoid inducible 55 kD protein or fragment thereof.
84. The method of claim 74, wherein said bodily fluid is selected from the group consisting of glaucomatous cell extract, fluid from the anterior chamber of the eye, blood, lymph and serum.
85. The method of claim 74, wherein said complementary nucleic acid molecule obtained from a cell or present in a bodily fluid of said patient is expressed by steroid-treated cells.
86. The method of claim 74, wherein said bodily fluid is ocular aqueous, and wherein said cells are HTM cells.
87. A method for diagnosing steroid sensitivity in a patient under evaluation for suspected steroid sensitivity which comprises assaying the concentration of a molecule, whose concentration is dependent upon the expression of a gene, said gene having a nucleic acid sequence which specifically hybridizes to SEQ ID NO: 3 and which encodes for a glucocorticoid inducible 66 kD glycosylated protein and a glucocorticoid inducible 55 kD protein, said molecule being present in a sample of cells or bodily fluid of said patient, in comparison to the concentration of that molecule present in a sample of cells or bodily fluid of an individual who does not have steroid sensitivity and is not predisposed to have steroid sensitivity, wherein an assayed concentration of said molecule is different from the assayed concentration of said molecule in said individual who does not have steroid sensitivity and is not predisposed to have steroid sensitivity is diagnostic of steroid sensitivity in said patient.
88. The method of claim 87, wherein said bodily fluid is selected from the group consisting of glaucomatous cell extract, fluid from the anterior chamber of the eye, blood, lymph and serum.
89. The method of claim 87, wherein said molecule is a protein molecule expressed by said gene.
90. The method of claim 87, wherein said molecule is an mRNA

molecule encoded by said gene, or a cDNA molecule encoded by said gene.

91. The method of claim 87, wherein said concentration of said mRNA molecule is assayed by incubating a sample of said bodily fluid in the presence of a nucleic acid molecule that hybridizes to said mRNA molecule.

92. The method of claim 87, wherein said expression of said gene is assayed by incubating a sample of said cells or said bodily fluid in the presence of antibodies elicited in response to immunization of an antibody-producing cell with a protein selected from the group consisting of a recombinantly produced glucocorticoid inducible 66 kD glycosylated protein, and recombinantly produced glucocorticoid inducible 55 kD protein, wherein said antibody molecule binds said recombinantly produced glucocorticoid inducible 66 kD glycosylated protein or said recombinantly produced glucocorticoid inducible 55 kD protein.

93. The method of claim 92, wherein said antibodies recognize a protein molecule expressed by steroid-treated human trabecular cells.

94. A method for diagnosing steroid sensitivity in a patient which comprises the steps:

(A) incubating under conditions permitting nucleic acid hybridization: a marker nucleic acid molecule, said marker nucleic acid molecule comprising a nucleic acid molecule that is linked to gene, said gene having a nucleic acid sequence which specifically hybridizes to SEQ ID NO: 3 and which encodes for a glucocorticoid inducible 66 kD glycosylated protein and a glucocorticoid inducible 55 kD protein, and a complementary nucleic acid molecule obtained from a cell or a bodily fluid of said patient, wherein nucleic acid hybridization between said marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient permits the detection of a polymorphism whose presence is predictive of a mutation affecting the level or pattern of said glucocorticoid inducible 66 kD glycosylated protein or said glucocorticoid inducible 55 kD protein in said patient;

(B) permitting hybridization between said marker nucleic acid molecule and said complementary nucleic acid molecule obtained from said patient; and

(C) detecting the presence of said polymorphism, wherein the detection of said polymorphism is diagnostic of steroid sensitivity.

95. The method of claim 94, wherein said level is predictive.

96. The method of claim 94, wherein said pattern is predictive.

97. The method of claim 94, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is genetically linked to said gene, and has the sequence of a polynucleotide of chromosome 1, q.

98. The method of claim 94, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is genetically linked to said gene, and has the sequence of a polynucleotide of chromosome 1, q21-26.

99. The method of claim 94, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is genetically linked to said gene, and has the sequence

of a polynucleotide of chromosome 1, q23-24.
100. The method of claim 94, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is physically linked to within 1 mb of said gene.
101. The method of claim 94, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is physically linked to within 100 kb of said gene.
102. The method of claim 94, wherein said marker nucleic acid molecule comprises a nucleotide sequence of a polynucleotide that is physically linked to within 10 kb of said gene.
103. The method of claim 94, wherein said marker nucleic acid molecule comprises a nucleic acid sequence which specifically hybridizes to SEQ ID NO: 3 and which encodes for a glucocorticoid inducible 66 kD glycosylated protein or fragment thereof and a glucocorticoid inducible 55 kD protein or fragment thereof.
104. The method of claim 94, wherein said bodily fluid is selected from the group consisting of glaucomatous cell extract, fluid from the anterior chamber of the eye, blood, lymph and serum.
105. The method of claim 94, wherein said complementary nucleic acid molecule obtained from a cell or present in a bodily fluid of said patient is expressed by steroid-treated cells.
106. The method of claim 94, wherein said bodily fluid is ocular aqueous, and wherein said cells are HTM cells.